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ARTICLE

Pediatric model-based dose optimization using a pooled exposure–response safety analysis for nivolumab and nivolumab plus ipilimumab combination in melanoma

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Abstract

An exposure–response (E–R) safety analysis was conducted across adult and pediatric (<18 years) studies to evaluate the potential impact of higher nivolumab and/or ipilimumab exposures in adolescents (≥12 to <18 years) versus adults with melanoma using the approved adult dosing regimens for nivolumab alone or in combination with ipilimumab. Data from 3507 patients across 15 studies were used to examine the relationship between nivolumab–ipilimumab daily average exposure and time to grade 2+ immune-mediated adverse events (gr2+ IMAEs). Results from the E–R safety model showed ipilimumab, but not nivolumab, exposure to be a statistically significant predictor of gr2+ IMAEs. Significant covariates included sex (41% higher risk for women than men), line of therapy (19% higher for first-line than later-line), and treatment setting (26% lower for adjuvant than advanced melanoma). Younger age and lower body weight (BW) were each associated with a lower risk of gr2+ IMAEs (hazard ratio [HR]: 0.830 for 15-year-olds versus 60-year-olds and 0.84 for BW 52 kg versus 75 kg). For adolescents with melanoma treated with nivolumab in the advanced or adjuvant settings, these results are supportive of nivolumab flat dosing regimens for adolescents greater than or equal to 40 kg and BW-based dosing for adolescents less than 40 kg. These results also support adult weight-based dosing regimens for nivolumab plus ipilimumab in adolescents with advanced melanoma. This analysis suggests that although higher exposures are predicted in adolescents with lower weight compared with adults, there is no predicted immune-mediated safety risk when treated with the approved adult dosing of nivolumab with/without ipilimumab.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Monoclonal antibodies are often dosed in pediatric patients using body weight (BW)-based dosing to avoid higher flat-dosing exposure in patients with low BW.

Based on clinical safety data from pediatric trials, model-based dose optimization may identify and justify alternative dosing regimens in adolescent/pediatric patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the exposure–response (E–R) relationship across a dataset of adult and pediatric patients to better understand the exposure-driven risk of safety in pediatric patients when using the approved adult dosing regimens in melanoma.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Based on E–R safety analyses, higher drug exposures observed in adolescents versus adults treated with the same nivolumab and/or ipilimumab dosing regimen are not predicted to result in an increased safety risk.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This work emphasizes the importance of conducting E–R safety analyses using pediatric data for model-informed dose optimization to justify deviating from strict pediatric exposure matching to adult when similar safety and efficacy for pediatric and adults is predicted.

INTRODUCTION

Pediatric melanoma (MEL) is a rare but challenging disease to treat because of limited access to new medications. The genomic profile of MEL tumors is similar in both pediatric and adult patients, suggesting that therapeutic targets for adults with MEL may be applicable to pediatric patients.[1,2] Immune checkpoint inhibitors have shown remarkable survival benefit in adults with MEL[3] and are currently being investigated in multiple clinical studies for pediatric malignancies.[4–6]

Nivolumab and ipilimumab are fully human immunoglobulin monoclonal antibodies that selectively block programmed death receptor-1 (PD-1)[7] and cytotoxic lymphocyte antigen-4 (CTLA-4; CD152),[8] respectively, thereby potentiating antitumor response. Nivolumab is approved as monotherapy in adults with advanced MEL (advMEL) and in the adjuvant MEL (adjMEL) setting given intravenously at 240 mg every 2 weeks (q2w) or at 480 mg every 4 weeks (q4w), as well as in combination with ipilimumab (3 mg/kg) for advMEL.[9–12] Ipilimumab monotherapy at 3 mg/kg every 3 weeks (q3w) is approved in adolescent patients with unresectable or metastatic MEL.[10] The exposure of nivolumab and ipilimumab in adolescents is predicted to be higher than in adults (unpublished data), making it essential to understand the exposure-driven safety risk in adolescents to ensure safe administration of these agents.

Several studies have evaluated nivolumab and ipilimumab in pediatric patients. Nivolumab or ipilimumab monotherapy (dosed by body weight [BW]) was shown to be safe and well-tolerated in patients with advanced solid tumors.[13–17] Nivolumab monotherapy showed clinical activity in lymphoma, but not in other common pediatric tumors (only 1 patient with MEL was included in this study).[14] Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg q3w (N3I1) for four cycles followed by nivolumab 3 mg/kg q2w was well-tolerated in pediatrics (age >4) with solid tumors and demonstrated clinical activity. However, a trend toward higher toxicity was noted in a smaller proportion of patients from the same study who received the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3) approved dosing regimen for adults with MEL.[13] Data from these studies, as well as those in adult patients treated in advMEL and adjMEL settings, where pharmacokinetic (PK) and exposure–response (E–R) efficacy and safety relationships were characterized, were combined to support dosing recommendations for nivolumab alone and/or combined with ipilimumab in adolescents with MEL.[18–24]

A greater understanding of the exposure-driven safety risk in adolescents is crucial to ensure the safe administration of these agents, particularly because of the overlapping toxicities of nivolumab and ipilimumab and the potentially higher exposure of these agents in adolescents (unpublished data). Previous use of population PK (PopPK) and E–R modeling to support posology changes in adults for nivolumab and nivolumab plus ipilimumab have been conducted.[25–27]

In this paper, we describe the development of an E–R safety model using a composite safety end point of grade 2+ immune-mediated adverse events (gr2+ IMAEs) and data from studies evaluating nivolumab monotherapy, ipilimumab monotherapy, and nivolumab plus ipilimumab in adult, young pediatric (<12 years) and adolescent (≥12

to <18 years) patients with various solid tumors, including advMEL and treatment in the adjMEL setting. The E–R model developed was used to predict the safety of the approved adult dosing regimens of these agents in adolescents with advMEL and in the adjMEL setting. Overall, understanding the safety and efficacy of nivolumab and ipilimumab in young pediatric and adolescent patients is crucial to identifying potential treatment options and to ensuring their safe administration.

METHODS

Analysis data

This E–R safety analysis was performed with data across 15 clinical studies from 3507 patients primarily with MEL treated in the advanced or adjuvant settings with a wide variety of nivolumab, ipilimumab, and nivolumab plus ipilimumab dose regimens (Table S1). The study population included 42 young pediatric and 55 adolescent patients.

PK data were analyzed using previously developed PopPK modeling in pediatric and adult oncology patients. The model was adequate to predict the Empirical Bayes estimates (EBEs) in both pediatric and adult populations (unpublished data). Time-varying daily average exposure (C_{avg}) metrics of nivolumab and ipilimumab were simulated using EBEs of PK parameters in adults and adolescents with advMEL and/or treated in the adjMEL setting. Daily C_{avg} was selected as the exposure metric because of differences in the duration of nivolumab and ipilimumab treatments, which made use of a single summary measure to represent the exposures challenging. Daily C_{avg} accounted for differences in concentrations throughout the dosing interval, enabling the assessment of different dosing regimens included among the studies pooled in this analysis (Figure S1).

Gr2+ IMAEs is a composite safety end point regardless of treatment with immune-modulating medications, which were available for all the nivolumab studies, but not the ipilimumab monotherapy studies. The ipilimumab studies reported immune-related adverse events (irAEs; defined using predefined Medical Dictionary for Regulatory Activities [MedDRA] preferred terms). Given the close relationship between the two terms and the lack of reported IMAE data in the ipilimumab studies, irAEs were used in place of IMAEs for ipilimumab monotherapy studies (Table S2).

Analysis methods

The relationship between nivolumab and/or ipilimumab exposure (daily C_{avg}) and time to first occurrence of gr2+ IMAEs was characterized by a semiparametric stratified Cox proportional hazards (CPH) model.[28] A CPH model was stratified by treatment (nivolumab monotherapy, ipilimumab monotherapy, and nivolumab plus ipilimumab) and compared with an unstratified model.

In the full model, different functional forms of exposure (linear- and log-transformed nivolumab and ipilimumab) were assessed, along with covariate effects such as age, BW, race, programmed cell death ligand-1 (PD-L1), lactate dehydrogenase (LDH), sex, Eastern Cooperative Oncology Group-performance status (ECOG-PS), line of therapy, and tumor type; baseline LDH was normalized to the upper limit of normal (ULN), as the ULN was not the same across all patients because of differences in clinical laboratories. The potential interaction effect of nivolumab and ipilimumab exposure was also evaluated. Additionally, different baseline hazards were assessed after accounting for the potential overlapping modulatory effects. The hazard expression tested in the full model is shown in Table S3.

Model selection was based on Bayesian information criteria (BIC).[29] The BIC was used to select the functional forms that provide the best fit to the data and to determine the significance of the interaction effect between nivolumab and ipilimumab exposure/treatment. BIC values were calculated using the following equation:

$$\mathrm{BIC} = -2 \bullet \mathrm{LL} + k \bullet \ln(n)$$

where LL is the maximized log-likelihood objective function value for the final model, k is the number of estimated parameters, and n represents the number of observations. The hazard of event (gr2+ IMAEs) in the CPH model was expressed as:

$$\lambda_{(t)} = \lambda_{i0}(t)\exp\left(\beta^T X_j\right)$$

where $\lambda_{i0}(t)$ is a vector of the baseline hazard and X_j is a vector of predictor variables, including time-dependent exposure and other covariates. The parameter vector β^T was estimated by maximum partial likelihood. An increased or decreased risk was determined based on HRs.

Model evaluation

The model was evaluated using a visual predictive check (VPC), which compared the model-predicted cumulative distributions of gr2+ IMAEs with the corresponding distribution determined by nonparametric Kaplan–Meier analysis of the data used in the model development. The CPH model was used to predict event probability for each individual and 1000 simulations were performed for each patient to construct the 90% prediction intervals (PIs) of the distribution.

Model application

Magnitude of time-varying exposure effects on gr2+ IMAEs

The model was applied to evaluate the magnitude of time-varying exposure effects of nivolumab and/or ipilimumab on gr2+ IMAEs in adolescent and adult populations; all covariates in the E–R model, except exposure, were assigned to the reference value. For nivolumab monotherapy, ipilimumab exposure was set to zero. The same method was used to evaluate the N1I3 combination with all covariates, except exposure, assigned to the reference value as described above.

Stochastic simulations of exposure were performed using an adolescent population created by random sampling from the National Health and Nutrition Examination Survey database[30]; the population included 800 virtual individuals aged 12 to less than 18 years, and their corresponding BW, lean body mass, sex, and race. Exposure in the adult population ($N = 500$) was performed with adult patients with MEL by random sampling of those included in the PopPK analysis.

Predictions of gr2+ IMAEs in advMEL and adjMEL settings for adolescents treated with the adult dose

The aforementioned 800 adolescent and 500 adult subjects' simulated daily C_{avg} for different dosing regimens and the CPH model was used to predict the cumulative probability of gr2+ IMAEs for each individual, the 90% PIs of the distribution were constructed. The covariates of exposure, BW, age, race, and sex were from the PopPK analysis, and the other covariates that were included in the CPH full model (ECOG-PS, line of therapy, PD-L1, and LDH) were all set to reference value.

All analyses were performed on Intel Xeon-based multi-core Central Processing Unit servers running Ubuntu 18.04 on Amazon Web Services. All exploratory data analyses, presentations of E–R safety analysis, VPCs, and model application simulations were performed using R (version 4.0.3), key packages (survival version 3.3-1, lattice version 0.20.41, and survminer version 0.4.9) with documentation found on cran.r-project.org.

RESULTS

E–R model development

The initial model was stratified by treatment according to the observed differences in the cumulative probabilities of gr2+ IMAEs between treatments and that all ipilimumab monotherapy studies may have a different baseline hazard given the use of a slightly different definition for irAEs as compared with the other treatments that used IMAE definitions (Figure S2). The treatment-stratified CPH models (of nivolumab monotherapy, ipilimumab monotherapy, and nivolumab plus ipilimumab) showed significantly lower BIC values compared with the unstratified models (Table S4).

The stratified full model, which included the linear nivolumab and ipilimumab daily C_{avg} with interactions and covariate effects, was identified as the best model based on a 9.08 BIC value decrease between the best and worst stratified models (Table S5). No significant interaction was observed between the significant covariates and nivolumab and ipilimumab exposure, indicated by all BIC values of interaction models being higher than the full model (Table S6). Although the BW covariate showed an interaction effect on ipilimumab exposure, the BIC value decreased by only 1.6; the maximum correlation of covariates in this model was 0.928, indicating the best model was the one without the BW covariate interaction (Table S6).

The model was validated through VPCs of the first occurrence of gr2+ IMAE stratified by adult, young pediatric, and adolescent patients. The VPC plots showed good agreement between the model-predicted cumulative probabilities and the observed probability of gr2+ IMAEs in the analysis data set (Figure S3A). Whereas gr2+ IMAEs were slightly underpredicted in the young pediatric population, the predictions for adolescents and adults were in good agreement with the observed data, indicating that the model provided a good characterization of the probability of gr2+ IMAEs in these populations. VPC plots of nivolumab monotherapy and combination therapy stratified by age group, BW quartiles, treatment setting, and treatment group are presented in Figure S3B–F.

Effect of covariates on the full model

Parameter estimates of the full E–R gr2+ IMAEs model are presented in Table 1. In the full model, no strong correlation was observed between parameters, and only a moderate correlation was observed between nivolumab and ipilimumab exposure (correlation coefficient of 0.602; Table S7). The model estimated a statistically significant effect of ipilimumab exposure on the risk of gr2+ IMAEs, as the 95% confidence intervals (CIs) did not include the null value. The HR of increased risk of gr+2 IMAEs per unit increase in exposure for ipilimumab after accounting for the potential effect of the other covariates was 1.008 (95% CI: 1.001–1.014), indicating that higher ipilimumab exposure is associated with a higher risk of gr2+

TABLE 1 Parameter estimates of the E–R of gr2+ IMAEs (full model).

Predictor[a]	Estimate	Standard error	RSE%[b]	Hazard ratio coefficient[c] (95% CI)[d]
Nivolumab daily C_{avg} (μg/mL)	−0.0004655	0.0009231	198.3	0.9995 (0.9977–1.001)
Ipilimumab daily C_{avg} (μg/mL)	0.007693	0.003228	41.96	1.008 (1.001–1.014)
Age (years)	0.00414	0.001987	47.99	1.004 (1–1.008)
Body weight (kg)	0.006033	0.00156	25.85	1.006 (1.003–1.009)
Line of therapy [≥2L:1L]	−0.2079	0.09439	45.41	0.8123 (0.6751–0.9774)
Treatment setting [adjMEL:MEL]	−0.2972	0.0889	29.91	0.7429 (0.6241–0.8843)
Treatment setting [others:MEL]	0.3119	0.207	66.36	1.366 (0.9105–2.05)
PD-L1 status [≥5%:<5%]	−0.02175	0.06456	296.8	0.9785 (0.8622–1.11)
PD-L1 status [missing:<5%]	−0.1229	0.08553	69.62	0.8844 (0.7479–1.046)
Performance status [≥1:0]	0.0877	0.06695	76.35	1.092 (0.9574–1.245)
Sex [female:male]	0.3423	0.05882	17.18	1.408 (1.255–1.58)
Race [Asian:white]	0.2104	0.2139	101.7	1.234 (0.8115–1.877)
Race [Black/African American:White]	−0.3134	0.4529	144.5	0.7309 (0.3008–1.776)
Race [others/unknown:White]	−0.3504	0.2276	64.97	0.7044 (0.4509–1.101)
Log LDH (×ULN)	−0.0209	0.04906	234.8	0.9793 (0.8895–1.078)
C_{avg} nivolumab:C_{avg} ipilimumab	−0.000549	0.000159	28.97	0.9995 (0.9991–0.9998)

Note: The significant covariates are highlighted in bold.

Abbreviations: 1L, first-line; 2L, second-line; adjMEL, adjuvant melanoma; C_{avg}, daily average exposure; CI, confidence interval; E–R, exposure–response; gr2+ IMAE, grade 2 or greater immune-mediated adverse event; LDH, lactate dehydrogenase; MEL, melanoma; PD-L1, programmed cell death-ligand 1; RSE, relative standard error; ULN, upper limit of normal.

[a]Continuous predictors units are in parentheses and categorical predictors by [comparator: reference].

[b]RSE = (100 * SE/|estimate|).

[c]Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group.

[d]The 95% CI = (Exp(Estimate − 1.96 * SE), Exp(Estimate +1.96 * SE)).

IMAEs. In contrast, the model-estimated coefficient for nivolumab exposure was slightly negative and not significant, indicating a lack of association between nivolumab exposures and the risk of gr2+ IMAEs. However, with combination therapy, the interaction between nivolumab and ipilimumab exposures was shown to be statistically significant with an HR of 0.9995 (95% CI: 0.9991–0.9998), indicating a synergistic effect of the combination on the exposure compared with each agent administered alone.

Figure 1 shows the magnitude of the estimated effects of categorical and continuous covariates (constant over time) in the full E–R model. The predicted probability of gr2+ IMAEs was 41% higher in women versus men (HR: 1.41, 95% CI: 1.25–1.58), increased with BW (HR: 0.87 and 1.24 for 5th percentile and 95th percentile of BW vs. median BW, respectively), was 19% higher in patients treated in first-line versus second- or later-line settings (HR: 0.812, 95% CI: 0.675–0.977), and was 26% lower in patients treated in the adjuvant versus the advanced settings. Age was shown to have a marginal effect on the risk of gr2+ IMAEs, as the lower bound of the 95% CI included one; however, the risk of gr2+ IMAEs increased with age, with HRs of 0.84 and 1.08 for the 5th and 95th percentiles of age versus median age, respectively. Given that the proportion of adult patients was disproportionately higher than adolescent/young pediatric patients in this population, the 5th percentile of age was 19.1 years. The risk of gr2+ IMAEs for an adolescent at median age 15 years was calculated to be 17% lower (HR: 0.830) than for an adult (median age 60 years). Other covariates including race, baseline LDH, PD-L1, and PS were not shown to be significant predictors of the risk of gr2+ IMAEs.

Nivolumab and ipilimumab exposure over time

Although the use of time-varying exposures avoids immortalized time bias, the exposure-dependence of the event cannot be visualized effectively because exposures are constantly changing.[31] Therefore, we generated predicted cumulative probabilities with nivolumab alone or with ipilimumab to examine the effect of nivolumab and

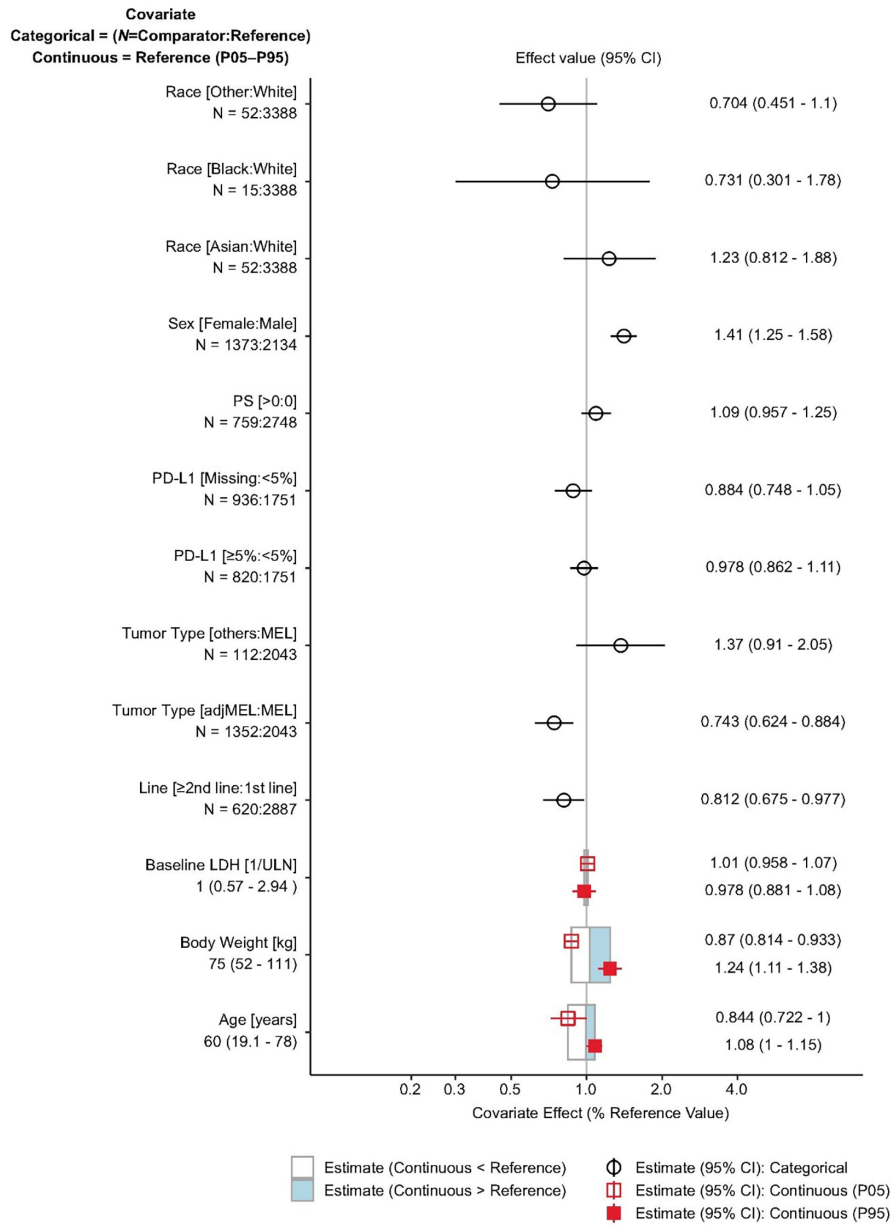

FIGURE 1 Estimated covariate effects of the E–R of gr2+ IMAEs (full model). Categorical [comparator: reference] (*n*) and continuous [reference] (P5 to P95) covariates are shown. P5 and P95 of continuous covariate effects (95% CI) are represented by horizontal width of open/shaded boxes (horizontal lines). The reference patient was a white male with a median normalized LDH value of 1, BW = 75 kg, age = 60 years, PS = 0, with first-line advMEL, and tumor cell PD-L1 less than 5%. The dataset includes a much larger number of adult patients compared with adolescent and pediatric patients; therefore, the P5 to P95 range for age is 19.1 to 78 years. adjMEL, adjuvant melanoma; advMEL, advanced melanoma; BW, body weight; CI, confidence interval; E–R, exposure–response; gr2+ IMAE, grade 2 or greater immune-mediated adverse event; LDH, lactate dehydrogenase; MEL, melanoma; P5, 5th percentile; P95, 95th percentile; PD-L1, programmed cell death ligand-1; PS, performance status; ULN, upper limit of normal.

ipilimumab exposure and their interaction effect on the risk of gr2+ IMAEs. The cumulative rate of gr2+ IMAE risk was higher with the nivolumab plus ipilimumab combination than with either agent administered alone, and was higher with ipilimumab monotherapy compared with nivolumab monotherapy (Figure 2a). There was minimal change in the predicted cumulative probability of gr2+ IMAEs for nivolumab monotherapy (3 mg/kg) across the 90% PI at each timepoint (Figure 2b). In contrast, a larger change in the predicted cumulative probabilities of gr2+ IMAEs across the 90% PI was noted for the N1I3 combination compared with nivolumab monotherapy; this was particularly evident after multiple doses of the combination, considering the range of nivolumab and ipilimumab daily C_{avg}, and the interaction between the agents (Figure 2c). This indicates a larger contribution of nivolumab and ipilimumab daily C_{avg} on the probability of gr2+ IMAEs for N1I3 relative to nivolumab monotherapy. However, E–R safety was relatively flat for the combination, with minimal change in predicted gr2+ IMAEs across the median (0.526), 5th (0.490), and 95th (0.558) percentiles at 12 weeks across ipilimumab exposure (Figure 2c).

E–R model application: nivolumab monotherapy in advMEL

To assess the risk of gr2+ IMAEs in adults and adolescents with advMEL and across various dosing schedules, several

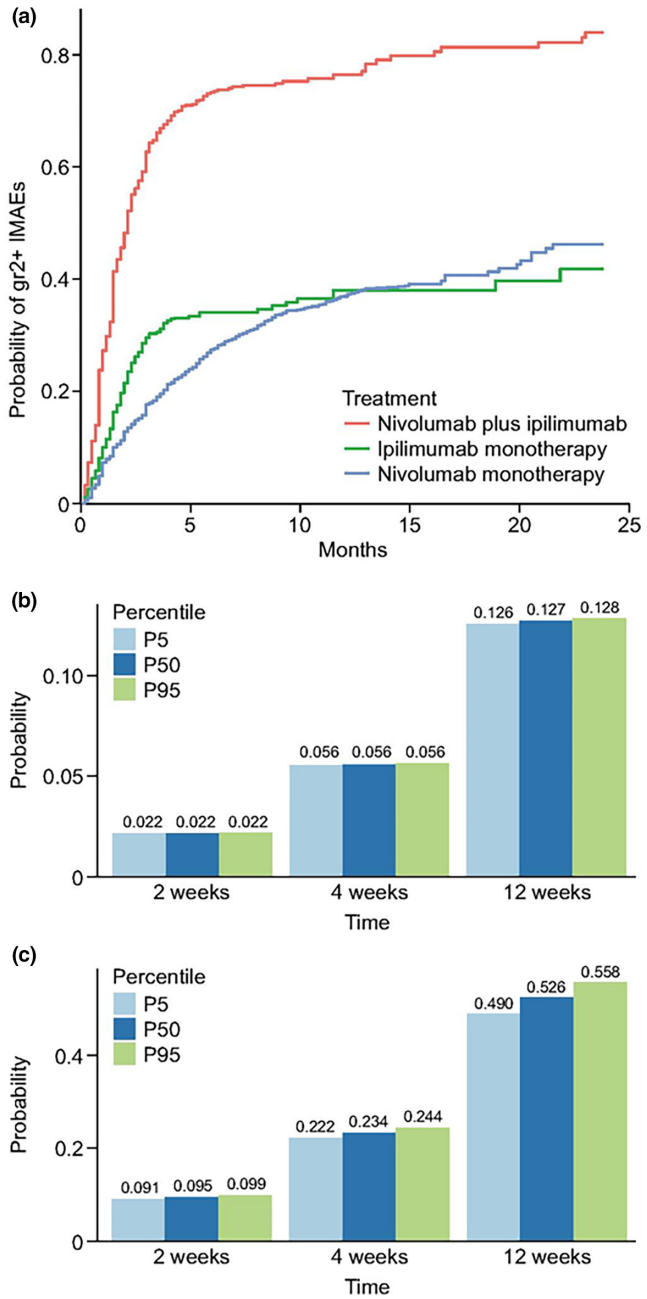

FIGURE 2 Illustration of the exposure effect of nivolumab and ipilimumab and their combination on the risk of gr2+ IMAEs. P5 and P95 probabilities were constructed by the simulated probability of 800 patients, where all covariates except exposure were assigned to the reference value (line of therapy = ≥second, treatment setting = advMEL, BLDHR = 10, PD-L1 = <5%, PS = 0, age = 50 years, BW = 50 kg, sex = female, race = white, ipilimumab exposure = 0). Time refers to the time after the first dose. (a) Estimated baseline hazard of the E–R of gr2+ IMAEs (full model). Baseline hazard was obtained by simulating a typical patient who received different treatments, where all of the covariates of the typical patient were assigned to the reference value (line of therapy = first-line, treatment setting = advMEL, BLDHR = 1, tumor PD-L1 < 5%, PS = 0, age = 50 years, BW = 75 kg, sex = male, race = White, ipilimumab exposure = 0, nivolumab exposure = 0). (b) Predicted cumulative probabilities (90% PI) of gr2+ IMAEs for nivolumab monotherapy (3 mg/kg) at selected timepoints. (c) Predicted cumulative probabilities (90% PI) of gr2+ IMAEs for nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) at selected timepoints. advMEL, advanced melanoma; BLDHR, baseline lactate dehydrogenase ratio; BW, body weight; E–R, exposure–response; gr2+ IMAE, grade 2 or greater immune-mediated adverse event; P5, 5th percentile; P50, 50th percentile; P95, 95th percentile; PD-L1, programmed cell death-ligand 1; PI, prediction interval; PS, performance status.

nivolumab monotherapy regimens were simulated in adults (240 mg q2w and 480 mg q4w) and in adolescents (3 mg/kg q2w for BW <40 kg or 240 mg q2w for BW ≥40 kg; 3 mg/kg q2w for all BW; 3 mg/kg up to 240 mg q2w [with cap]; 6 mg/kg q4w for BW <40 kg or 480 mg q4w for BW ≥40 kg; 6 mg/kg q4w for all BW; and 6 mg/kg up to 480 mg q4w [with cap]). The predicted gr2+ IMAEs for adolescent patients were shown to be similar across all q2w and q4w regimens with or without the dosage cap (Figure 3a,b). The risk of gr2+ IMAEs was generally higher for adults than for adolescents with advMEL, with overlapping 90% PIs (Table 2). In addition, predicted gr2+ IMAEs for adolescents remained lower than for adults across BW quartiles and BW ranges (Figure S4).

E–R model application: Nivolumab in combination with ipilimumab in the advMEL setting

The risk of gr2+ IMAEs for nivolumab plus ipilimumab for patients with advMEL was assessed in various simulated dosing regimens in adults (N1I3 q3w for 4 doses, then nivolumab 240 mg q2w or 480 mg q4w) and adolescents (N1I3 q3w for 4 doses, then nivolumab 3 mg/kg for BW <40 kg or 240 mg for BW ≥40 kg q2w or 6 mg/kg for BW <40 kg or 480 mg for BW ≥40 kg q4w; nivolumab 1 mg/kg [up to 80-mg cap] plus ipilimumab 3 mg/kg [up to 240-mg cap] q3w for 4 doses, then nivolumab 3 mg/kg [up to 240-mg cap] q2w or nivolumab 6 mg/kg [up to 480-mg cap] q4w).

The predicted risk of gr2+ IMAEs was similar between the two evaluated dosing regimens in adolescent patients (Figure 3c,d). In addition, the risk of gr2+ IMAEs with nivolumab plus ipilimumab was generally higher for adults than for adolescents, with overlapping 90% PIs (Table 2). As with nivolumab monotherapy, this result was consistent across BW ranges and the predicted risk of gr2+ IMAEs for adolescents remained lower than that for adults across BW quartiles (Figure S5).

E–R model application: nivolumab monotherapy in the adjMEL setting

As with advMEL, various nivolumab monotherapy regimens were simulated in adolescents and adult patients

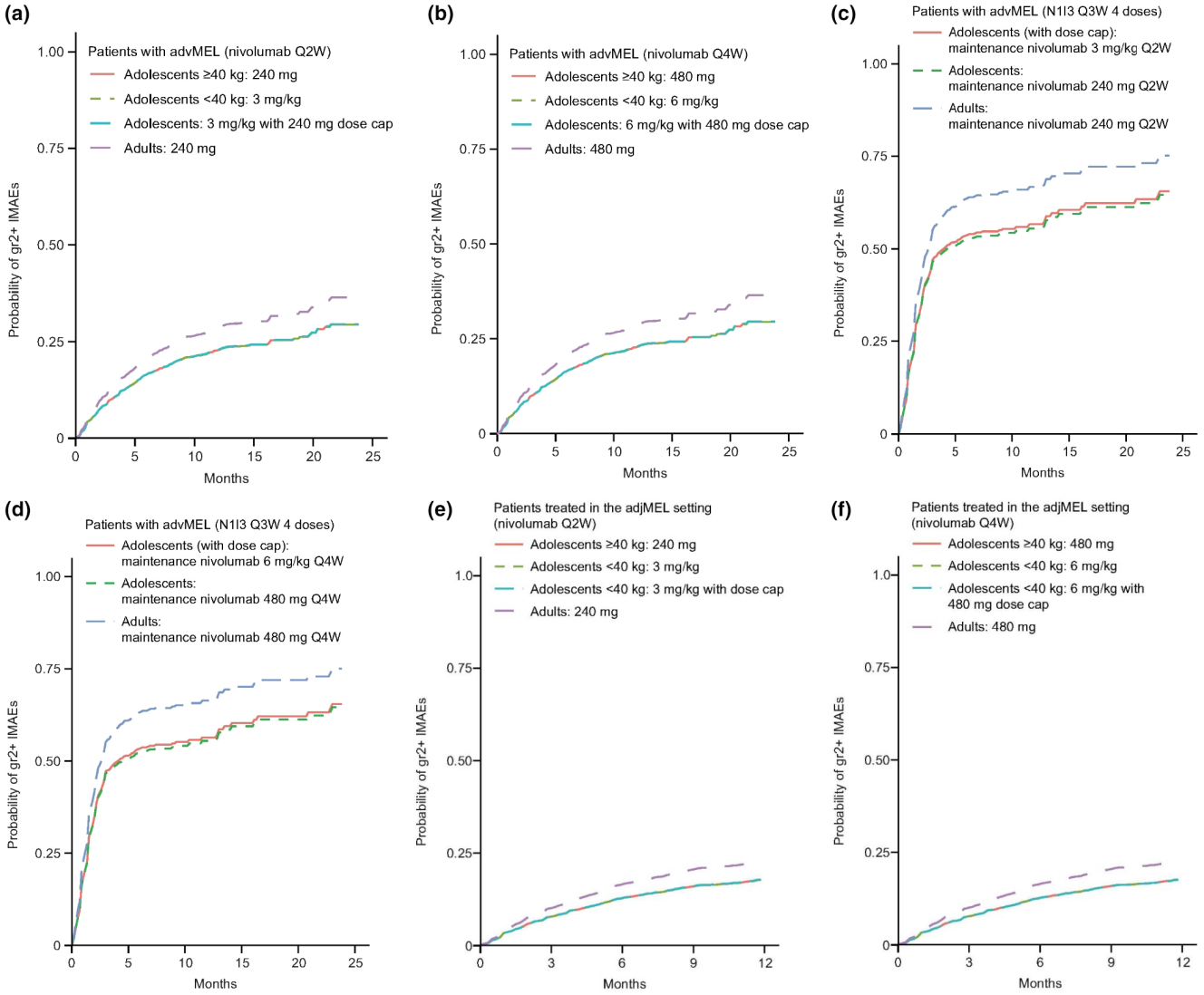

FIGURE 3 Predicted median cumulative probability of gr2+ IMAEs using predicted time-varying daily C_{avg}. (a) Nivolumab q2w dosing regimens in adult and adolescent patients in the advMEL setting. A dose cap of 240 mg was applied to nivolumab. Adolescent patients received nivolumab 3 mg/kg q2w (<40 kg) or 240 mg q2w (≥40 kg). (b) Nivolumab q4w dosing regimens in adult and adolescent patients in the advMEL setting. A dose cap of 480 mg was applied to nivolumab. Adolescent patients received nivolumab 6 mg/kg q4w (<40 kg) or 480 mg q4w (≥40 kg). (c) Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3) q3w for four doses, followed by nivolumab 240 mg q2w in adults and adolescents in the advMEL setting. A dose cap of 80 mg was applied to nivolumab and of 240 mg applied to ipilimumab. (d) N1I3 q3w for four doses, followed by nivolumab 480 mg q4w in adults and adolescents in the advMEL setting. A dose cap of 80 mg was applied to nivolumab and 240 mg applied to ipilimumab. (e) Nivolumab Q2W dosing regimens in adult and adolescent patients in the adjMEL setting. A dose cap of 240 mg was applied to nivolumab. Adolescent patients in the adjMEL setting received nivolumab 3 mg/kg q2w (<40 kg) or 240 mg q2w (≥40 kg). (f) Nivolumab q4w dosing regimens in adult and adolescent patients in the adjMEL setting. A dose cap of 480 mg was applied to nivolumab. Adolescent patients in the adjMEL setting received nivolumab 6 mg/kg q4w (<40 kg) or 480 mg q4w (≥40 kg). Predictions are across the BW range for adolescents (29.3 kg to 154.8 kg) and adults (40.3 kg to 159.9 kg). adjMEL, adjuvant melanoma; advMEL, advanced melanoma; BW, body weight; C_{avg}, daily average exposure; gr2+ IMAE, grade 2 or greater immune-mediated adverse event; M, maintenance dose; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks.

in the adjMEL setting. Results were similar to those observed with advMEL; the predicted risk of gr2+ IMAEs was similar for adolescent patients across regimens (Figure 3e,f). In the adjMEL setting, the risk of gr2+ IMAEs was higher for adults than for adolescents, with overlapping 90% PIs (Table 2). Results were consistent across different BW ranges and BW quartiles (Figure S6).

DISCUSSION

The clearance and volume of monoclonal antibodies are significantly influenced by BW, making dose adjustment in pediatric patients based on BW or BW tiers a common practice.[32] However, flat dosing, as used for nivolumab monotherapy, requires additional

TABLE 2 Model predicted median probability (90% PI) of gr2+ IMAEs at select times.

Patient	Age–dosing group	Time		
		6 months	1 year	2 years
Advanced MEL	Adult 240 mg	0.207 (0.17–0.267)	0.286 (0.237–0.364)	0.365 (0.305–0.456)
	Adolescent Nivo 3 mg/kg q2w (<40 kg) or 240 mg (≥40 kg) q2w	0.164 (0.105–0.224)	0.229 (0.149–0.307)	0.295 (0.195–0.39)
	Adolescent 3 mg/kg	0.164 (0.106–0.226)	0.229 (0.15–0.311)	0.295 (0.197–0.393)
	Adolescent Nivo 3 mg/kg (up to 240 mg) q2w	0.165 (0.106–0.226)	0.23 (0.15–0.311)	0.296 (0.197–0.393)
	Adult 480 mg	0.207 (0.17–0.267)	0.286 (0.237–0.364)	0.365 (0.305–0.457)
	Adolescent Nivo 6 mg/kg q4w (<40 kg) or 480 mg (≥40 kg) q4w	0.164 (0.105–0.223)	0.229 (0.149–0.307)	0.295 (0.195–0.390)
	Adolescent 6 mg/kg	0.164 (0.106–0.225)	0.229 (0.15–0.311)	0.295 (0.197–0.393)
	Adolescent cap Nivo 6 mg/kg (up to 480 mg) q2w	0.165 (0.106–0.227)	0.23 (0.151–0.312)	0.297 (0.198–0.394)
	Adult Nivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 240 mg q2w	0.635 (0.553–0.743)	0.667 (0.585–0.773)	0.752 (0.671–0.846)
	Adolescent Nivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 3 mg/kg (<40 kg) or 240 mg (≥40 kg) q2w	0.525 (0.371–0.653)	0.555 (0.396–0.684)	0.646 (0.474–0.769)
	Adolescent Nivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 3 mg/kg (up to 240 mg) q2w[a]	0.536 (0.381–0.662)	0.566 (0.406–0.694)	0.656 (0.483–0.778)
	Adult Nivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 480 mg q4w	0.629 (0.548–0.739)	0.521 (0.368–0.648)	0.531 (0.376–0.657)
	Adolescent Nivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 6 mg/kg (<40 kg) or 480 mg (≥40 kg) q4w	0.662 (0.581–0.77)	0.553 (0.392–0.681)	0.562 (0.401–0.69)
	AdolescentNivo 1 mg/kg + Ipi 3 mg/kg q3w for 4 doses, then Nivo 6 mg/kg (up to 480 mg) q4w[a]	0.748 (0.667–0.843)	0.644 (0.472–0.766)	0.653 (0.479–0.775)
Adjuvant treatment of MEL	Adult 240 mg	0.162 (0.128–0.209)	0.225 (0.18–0.287)	—
	Adolescent Nivo 3 mg/kg q2w (<40 kg) or 240 mg (≥40 kg) q2w	0.125 (0.0795–0.172)	0.175 (0.113–0.239)	—
	Adolescent 3 mg/kg	0.125 (0.0804–0.173)	0.175 (0.114–0.24)	—
	Adolescent Nivo 3 mg/kg (up to 240 mg) q2w	0.126 (0.0804–0.174)	0.176 (0.114–0.241)	—
	Adult 480 mg	0.162 (0.128–0.209)	0.225 (0.18–0.287)	—
	Adolescent Nivo 6 mg/kg q4w (<40 kg) or 480 mg (≥40 kg) q4w	0.125 (0.0793–0.172)	0.175 (0.113–0.238)	—
	Adolescent 6 mg/kg	0.125 (0.0803–0.173)	0.175 (0.114–0.24)	—
	Adolescent Nivo 6 mg/kg (up to 480 mg) q4w	0.124 (0.0797–0.172)	0.175 (0.113–0.239)	—

Abbreviations: gr2+ IMAE, grade 2 or greater immune-mediated adverse event; MEL, melanoma; PI, prediction interval; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks.

[a]Dose cap of 80 mg applied to nivolumab and 240 mg applied to ipilimumab for the first 4 doses.

consideration in lower BW pediatric patients because their exposures may exceed those of adults. In addition to the effect of BW, a recent PK assessment of pediatric patients dosed with nivolumab and ipilimumab alone or in combination reported age-related lowering of clearance and incremental increases in exposure compared with adults (unpublished data). To evaluate the risk of exposure-driven safety associated with nivolumab and ipilimumab and to optimize dosing in adolescents with advMEL or in the adjMEL setting, this pooled E–R safety analysis was conducted based on data from 3507 patients. The impact of higher exposure on efficacy in adolescents versus adults was not assessed based on the following rationale: nivolumab and ipilimumab E–R efficacy relationships are relatively flat; the similarity of disease in adults and adolescents with melanoma; and the expectation that higher adolescent exposures will not have a negative impact on efficacy. Gr2+ IMAEs was

selected as the endpoint because previous E–R safety analyses in adults have shown it to be a more sensitive composite safety end point to evaluate exposure risk.[27,33]

The E–R model provided an adequate description of the cumulative probability of the time to first occurrence of a gr2+ IMAE in adult and adolescent patients in the advMEL or adjMEL setting. The use of a stratified baseline hazard significantly improved the model by decreasing the BIC value. The addition of the treatment strata function provided a meaningful statistical improvement in the full model by differentiating the effects of monotherapy from those of the combination and evaluating the interaction between nivolumab and ipilimumab exposure, specifically for the combination.[34,35] The baseline cumulative rate of the risk of gr2+ IMAEs was higher in the nivolumab plus ipilimumab group compared with either monotherapy group and was higher with ipilimumab alone compared with nivolumab alone through the first 5 months.

The risk of gr2+ IMAEs was adequately described by a linear functional form of nivolumab and ipilimumab daily C_{avg} with interaction. After accounting for the potential effect of other covariates, ipilimumab exposure and the interaction between nivolumab and ipilimumab in the combination regimen were significant predictors of gr2+ IMAE risk. Higher ipilimumab exposure was associated with a higher risk of gr2+ IMAEs, and higher nivolumab and ipilimumab exposure were associated with a higher probability of gr2+ IMAEs for combination relative to nivolumab exposure for nivolumab monotherapy. Adolescent safety was well-predicted by the model, but underpredicted young pediatric (Figure S3). This could be due to lower subject numbers ($N=42$ for young pediatric vs. $N=55$ for adolescents) and/or due to covariate effects that are not currently included. Future model development will be needed to support dosing recommendations for the young pediatric population. Various BW-based and flat dosing scenarios for nivolumab monotherapy were simulated for adolescent patients, with the adult flat-dosing exposure used as a target. For adolescent flat dosing scenarios, a flat dose may be appropriate for patients who weigh greater than or equal to 40 kg (median BW of a 12-year-old) due to potential for higher exposures in adolescents weighing less than 40 kg versus adults. However, a different BW threshold could be supported based on E–R relationships, therapeutic margins, and the benefit: risk assessment conducted by each individual health authority. Although BW-based dosing was originally approved and flat dosing is currently approved for nivolumab,[9] the flat dosing range was selected as the reference because the exposure range was wider than the adult weight-based exposure range. Predicted gr2+ IMAEs for adolescent patients with advMEL and in the adjMEL setting were similar across the evaluated dosing regimens, with and without a dose cap. In addition, gr2+ IMAEs are generally higher for adults than for adolescents in the advMEL and adjMEL settings, with overlapping 90% PIs. This may be due to age and BW being significant predictors, with higher risk associated with higher BW and older age. The moderate increase in exposure in adolescents relative to adults does not result in an increased risk of gr2+ IMAEs in adolescents, the flat nivolumab E–R being a contributing factor. Therefore, the result is consistent across different BW ranges, where predicted gr2+ IMAEs for adolescents remains lower than that of adults across the BW quartiles (Figures S4 and S6).

For nivolumab plus ipilimumab with nivolumab q2w or q4w maintenance dosing, the range for adult weight-based dosing exposure is narrower than that of adolescents. The predicted gr2+ IMAEs for adolescent patients are similar between the two evaluated dosing regimens (with and without a dose cap). Additionally, the gr2+ IMAEs are generally higher for adults than for adolescents, with overlapping 90% PIs. This may be due to age and BW being significant predictors, with higher risk being associated with higher BW and older age. The effect of both nivolumab and ipilimumab exposures when dosed in combination is relatively flat; therefore, the moderate exposure increases in adolescent patients relative to adults is not predicted to result in an increased risk of gr2+ IMAEs. The result is consistent across different BW ranges, as shown in Figure S5.

In conclusion, these results report similar predicted probabilities of gr2+ IMAEs for adolescent patients across the evaluated nivolumab and ipilimumab dosing regimens, providing a data-driven rationale to deviate from strict exposure matching to adults for the recommended dose in adolescents. The moderate increase in exposure in adolescents relative to adults for patients with low BW (when considering flat-dose nivolumab monotherapy) and for patients with high BW (when considering BW-based dosing with the nivolumab plus ipilimumab combination) was not predicted to result in an increased risk of gr2+ IMAEs. There is no predicted immune-mediated safety risk when adolescents are treated with the approved adult dosing regimens for nivolumab with or without ipilimumab. This study indicates that BW plays a role in the observed difference in both PK profiles (manuscript in review) and safety outcomes (independent of exposure considerations). This highlights the critical importance of not relying solely on exposure-matching during drug development for pediatrics. Nivolumab and nivolumab with ipilimumab were ultimately approved for the treatment of adolescents with melanoma in the United States and the European Union based on this analysis. However, the

BW threshold for adolescent flat dosing for nivolumab monotherapy was greater than or equal to 40 kg in the United States and greater than or equal to 50 kg in the European Union and reflects the individual health authority's assessment of benefit:risk.

AUTHOR CONTRIBUTIONS

S.D. and L.H. wrote the manuscript.; S.D., L.H., L.Z., Y.Z., A.R., and J.S designed the research. S.D., Z.H., and S.L. performed the research. S.D., L.H., L.Z., Y.Z., A.R., and J.S. analyzed the data. Bristol-Myers Squibb's policy on data sharing can be found at https://www.bms.com/researchers-andpartners/independent-research/data-sharing-request-process.html.

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CONFLICT OF INTEREST STATEMENT

All authors are employees and stock shareholders of Bristol Myers Squibb.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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